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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,628	03/01/2004	Benjamin G. Davis	GC571-2-C1	3111

7590 05/02/2006

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94034-1013

EXAMINER	
PATTERSON, CHARLES L JR	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,628	DAVIS ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004 and 27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-145* is/are pending in the application.

4a) Of the above claim(s) *11-18,48-55 and 74-145* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,19-47 and 56-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claim 1-10, 19-47 and 56-73 drawn to a catalytic antagonist attached to a subtilisin in the reply filed on 2/27/06 is acknowledged. The traversal is on the ground(s) that there would not be a serious burden upon the examiner to examine Groups I-VIII and XI because each is directed to proteases or enzymes that cleave proteins, or alternatively that groups I-III be examined together because each is a serine protease. This is not found persuasive because, as stated in the restriction requirement, "[t]hese claims are directed to catalytic antagonists that can be an almost endless list of chemical compounds". The examiner restricted the claims to the moiety that the "targeting moiety" was attached to but in reality the "targeting moiety" could be an almost endless number of chemical compounds. Secondly, the enzymes of the different groups are different enzymes with different characteristics. Therefore it is maintained that there would be a significant burden upon the examiner to search all of the claims referred to and the restriction is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-18, 48-55 and 74-145, and claims 1-10, 19-47 and 56-73 not drawn to an antagonist attached to subtilisin, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/27/06.

The disclosure is objected to because of the following informalities:

Throughout the specification and in several of the figures the abbreviation "SBL" is used but is apparently not defined anywhere. Apparently "SBL"

is the abbreviation for "subtilisin" and should be defined at least in the first instant of its use, e.g. on page 4, line 9.

On page 18, line 5, the description of Figure 19 lacks a verb. Perhaps "is a" should be inserted between "19" and "plot".

Appropriate correction is required.

Claims 19, 34-35, 59-60 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite in the recitation of "said target" in that there is no antecedent basis for this term. Substituting "said target molecule" for the instant recitation would overcome this rejection.

Claim 34 is confusing in the recitation of "wherein targeting", which should apparently be "wherein said targeting".

Claims 35 and 72 are confusing in the recitation of "-thioethyl". It is not clear what the hyphen is meant to indicate.

Claims 59-60 are grammatically incorrect in the recitation of "is component", which should be "is a component".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims refer to particular residue positions in a *Bacillus lentus* subtilisin. There is no sequence disclosure in the instant application and therefore one of ordinary skill in the art reading this specification would not know what particular sequence was being referred to. This is considered "essential matter" to these claims. Applicants may add the sequence to the specification if they can show it was known in the prior art.

Claims 1-10, 19-47 and 56-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 25 and 62 refer to a "cognate ligand". It is not seen where this is defined in the specification such that one of ordinary skill in the art would know what the mete and bounds of this term is.

Reference is made throughout the specification to "GC36-WT". While it is presumed that this refers to some wild-type subtilisin, this is not apparently stated anywhere in the specification. Understanding that this is a wild-type subtilisin is essential to understanding the data presented in the specification. Applicants should define the term, showing where in the prior art this term is used if in fact it is defined in the specification.

It is not seen where the specification shows that after the targeting moiety degrades the target molecule, it is released to bind to another target molecule, as required by the instant claims. For example in Example 3, page 67, the "S166C-pyrazole", which is apparently the catalytic antagonist, is

present at 3.4 :M concentration while the HLADH, apparently the target molecule, is present at 2.62 :M. Therefore the catalytic antagonist is in molar excess to the target molecule and showing a reduction in HLADH activity would not indicate that when one molecule of S166C-pyrazole had bound to one molecule of HLADH, the subtilisin degraded the HLADH molecule and then the S166C-pyrazole became unbound and then acted on another molecule. With the subtilisin molecule being in access it could just bind and degrade the HLADH and remain bound to it and the same data be obtained. The data in Table 11 apparently does not refute this assertion as after 3 hours the percentage activity with the S166C-pyrazole was greater than the same time in Table 7, even though the S166C-pyrazole is present in sub-stoichiometric amounts to the HLADH.

Example 1, Table 2 and Example 9, Table 30 show "Amidase Kinetics" and "ESMS". Example 11, Table 44 shows "Amidase activity". Exactly what these labels represent and the significance of them in measuring the effectiveness of Pyrazole-CMM and Biotin-CMM, which are presumed to mean subtilisin mutants attached to pyrazole and biotin, respectively, is not understood. An explanation is required. Applicants show "Amidase Kinetics" and "Esterase Kinetics" with the "Biotin-CMMs" (Tables 30 and 31). Exactly what does amidase and esterase activity have to do with biotin? The significance of this is not understood. In discussing Table 31 applicants state that "[t]he biotin-CMMs have an approximately four fold lower k_{cat} compared to SML-WT with the S156C-S-Biotin CMM the only exception" and that it is "about two fold lower that for SBL-WT". If one looks at the first set of numbers under the column headed "k_{cat}", then this appears to be the case (e.g. 825 vs. 1940) but if one looks at the set of numbers after that (e.g. 42.7 vs. 180) then this is not true. All three columns in Table 31 have two sets of numbers and it is ap-

parently not disclosed what these two sets of numbers are. In their reply to this characterization in the parent application, applicants state that "the unknown quantity in 'Table 31'…refers to margins of error". If this is true then the Table should be changed to indicate this, being sure not to add new matter. As it is now the table does not indicate to one of ordinary skill in the art that some of the values are margins of error. Perhaps the same thing also applies to the three columns under "Amidase Kinetic" in Table 30. Applicants could possibly refer to Table 2, which is similar to Tables 30 and 31 in this regard. This table has the three columns under "Amidase Kinetics" labeled with margins of error. Perhaps there are also other places in the specification that applicants could point to that would indicate that the values in Tables 30 and 31 are supposed to be margins of error.

On page 93, lines 2-3, it is disclosed that "suc-AAPF-SBn" is used as substrate to assay biotin-modified subtilisin for amidase. Apparently it is not disclosed what "suc-AAPF-SBn" is so that the significance of this assay cannot be ascertained.

Claims 1-7, 19-28, 37-42, 44 and 56-65 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for subtilisin, does not reasonably provide enablement for the other embodiments of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

All of the embodiments in the instant specification that have been shown to be operable using mutants of subtilisin and one of ordinary skill in the art is not taught by the specification how to make any other catalytic antagonists or where to attach the targeting moiety to any other enzyme. An-

other enzyme bound to a targeting moiety through a cysteine residue may well not have any activity and therefore the claims should be limited to subtilisin.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Chandrasegaran (A). The instant reference teaches in column 7, lines 23-30 that FokI restriction endonuclease has two separate domains, a nuclease cleavage domain and a sequence recognition domain. This teaching alone would read on the instant claims as written since there is no requirement that the "enzyme" and the "targeting moiety" come from different original molecules and the phrase "targeting moiety being attached to an enzyme" reads on the intact enzyme as the two regions are attached by a chemical bond, i.e. a peptide bond. The reference further teaches that when the cleavage domain of the enzyme is linked to the *Drosophila* Ultrabithorax homeodomain (Ubx) the enzyme will bind according to Ubx and cleave according to the cleavage domain. This embodiment would read on the claims when the two moieties come from different sources.

Davis, et al. (U) and Epenetos, et al. (N) are cited as of interest. These reference were cited in the parent application as teaching proteins with enzymes and targeting moieties, but applicant convinced the examiner

that these reference did not read on the instant claims because among other things they did not teach degrading of the target molecule and release of the antagonist to bind and degrade another molecule. However, see reference to this in the 35 USC § 112 first paragraph rejection *supra*, where it is stated the there is no evidence in the specification that the antagonists taught here will degrade and bind to another molecule.

Copies of Epenetos and Davis are not being sent because they were cited in the parent application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 571-272-0936. The examiner can normally be reached on Monday - Friday from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the

Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
May 1, 2006